Cost-effectiveness of microscopy of urethral smears for asymptomatic Mycoplasma genitalium urethritis in men in England

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Introduction

Over the past decade, there has been a change in the clinical investigation and management of men attending sexual health services in the UK. Previously, all men, regardless of symptoms, underwent urethral smears, a process by which a sample is taken from inside the urethra and Gram stained for examination by light microscopy (1). This allowed for the immediate diagnosis of two conditions: presumptive gonorrhoea and non-gonococcal urethritis (inflammation of the urethra in the absence of gonorrhoea). Men with either of these conditions, and their sexual partners, were then offered immediate treatment with appropriate antibiotics whilst waiting several days for more definitive results.

With the widespread use of sensitive and specific non-invasive urine testing for chlamydia and gonorrhoea, and in order to streamline services in line with emerging evidence that it is not needed, guidelines now recommend only performing urethral microscopy in symptomatic men (1). A consequence of this change in practice is that asymptomatic men with urethritis,

caused by neither chlamydia nor gonorrhoea (known as non-chlamydial, non-gonococcal urethritis or NCNGU), no longer receive empirical antimicrobial therapy. Their sexual partners are also left untreated. However, at the time of the most recent national audit (1), a small number of clinics continued to provide routine urethral microscopy to asymptomatic men, contrary to the guidelines.

The potential impact of this change in practice on costs and patients outcomes is not clear and has not yet been explored in any depth. Asymptomatic urethritis has many causes, both infectious and non-infectious (1). Notably, *Mycoplasma genitalium* is present in 8-10% of men with asymptomatic urethritis (1) and is associated with both cervicitis and pelvic inflammatory disease in women (2). There is limited access to testing for *M. genitalium* in the UK and few men are tested for this organism. Therefore, whereas previously, men with asymptomatic urethritis secondary to *M. genitalium* and their partners may have received successful treatment as part of empirical therapy for urethritis, this is no longer the case.

The focus of this study is on the potential cost implications of this change in clinical practice assuming that some men with asymptomatic NCNGU have *M. genitalium*, which can have adverse and costly reproductive health outcomes in their female sexual partners. Specifically, the objective of this economic evaluation is to determine whether the screening landscape at the time of the last national audit, in which a small number of clinics continued to perform routine microscopy in asymptomatic men is a cost-effective approach to diagnosing and treating asymptomatic NCNGU compared to the national guideline recommending not performing microscopy for this patient group. While it is acknowledged that there may be other causes of asymptomatic NCNCU other M. *genitalium*, there is little robust evidence that some of these may lead to important potential consequences. A previous study by Saunders et al. (2011) (3) found a paucity of high quality evidence that asymptomatic NCNGU is associated with significant consequences for men or their sexual partners. Thus, this study only considers cases caused by M. *genitalium*.

Methods

In order to estimate the impact of testing and treatment on the future transmission of possible significant pathogens responsible for asymptomatic NCNGU it is necessary to use an appropriate modelling approach for infectious diseases which can describe the transmission of *M genitalium* between individuals, namely a transmission dynamic model (TDM) (4, 5). In this study a TDM describing the transmission of *M genitalium* in the population of 16-30 year olds in England was constructed in order to examine changes in the use of urethral microscopy in asymptomatic men in genitourinary medicine (GUM) clinics. Here, the model output provides a hypothetical model state for asymptomatic patients which are defined here as those that do not have any symptoms associated with M. *genitalium* but who may present seek care following partner notification or who may spontaneously seek screening. This economic evaluation uses outputs from this model, along with secondary data describing resource use and takes the form of a cost-effectiveness analysis carried out from a health care provider perspective, with costs valued at 2014/2015 UK prices.

Model structure

The output used in this economic analysis is taken from a TDM which has been described in full elsewhere (6). In brief, this is a compartmental transmission model of the natural history of *M genitalium*, its diagnosis, and treatment levels, and thus only *M genitalium* was considered in this cost-effectiveness analysis. Heterogeneous sexual behaviour is described in the model which was parameterised by behaviour data from a number of key UK surveys, national surveillance data, and with the natural history of NCNGU being informed from data in the literature. The model describes the incidence and prevalence of symptomatic and asymptomatic infection, PID, care-seeking behaviour due to symptoms, partner notification, and the possibility of treatment failure. The uncertainty of the parameters in the model was also factored into the model parameterisation.

The time horizon for the economic analysis is 20 years, although this is subject to sensitivity analysis. It was felt that a time horizon longer than this would not be appropriate due to the inevitable changes to testing technology and approaches to offering STI screening to the population in the future. A discount rate of 3.5% was applied to costs and outcomes in accordance with NICE guidelines (7).

All settings where sexual health services are provided were initially considered for inclusion in this analysis. However, guidelines detailing the specific pathways and resources used at different sexual health service settings were sparse with the most reliable clinical data and cost data found in the literature being related to general practice (GP) and GUM settings, with GP consultations being considered due to the possibility of referral onwards to GUM services for further management. In this study the methodological focus is narrowed to the diagnosis and treatment of NCNGU in general practice and GUM clinics.

Testing Pathways for Economic analysis

Three different pathways are compared in terms of their resource use and costs, each representing alternative approaches to the testing and treatment of patients with asymptomatic NCNGU. These pathways represent: 1) the current recommended practice of not offering microscopy to asymptomatic men in GUM settings; 2) offering a small proportion (5%) of asymptomatic men microscopy (i.e. men attending a small number of GUM services) ; and 3) offering microscopy to all asymptomatic men attending all GUM services. These three pathways are referred to in this study as ‘Current Recommended Practice’, ‘5% Microscopy’, and ‘100% Microscopy’.

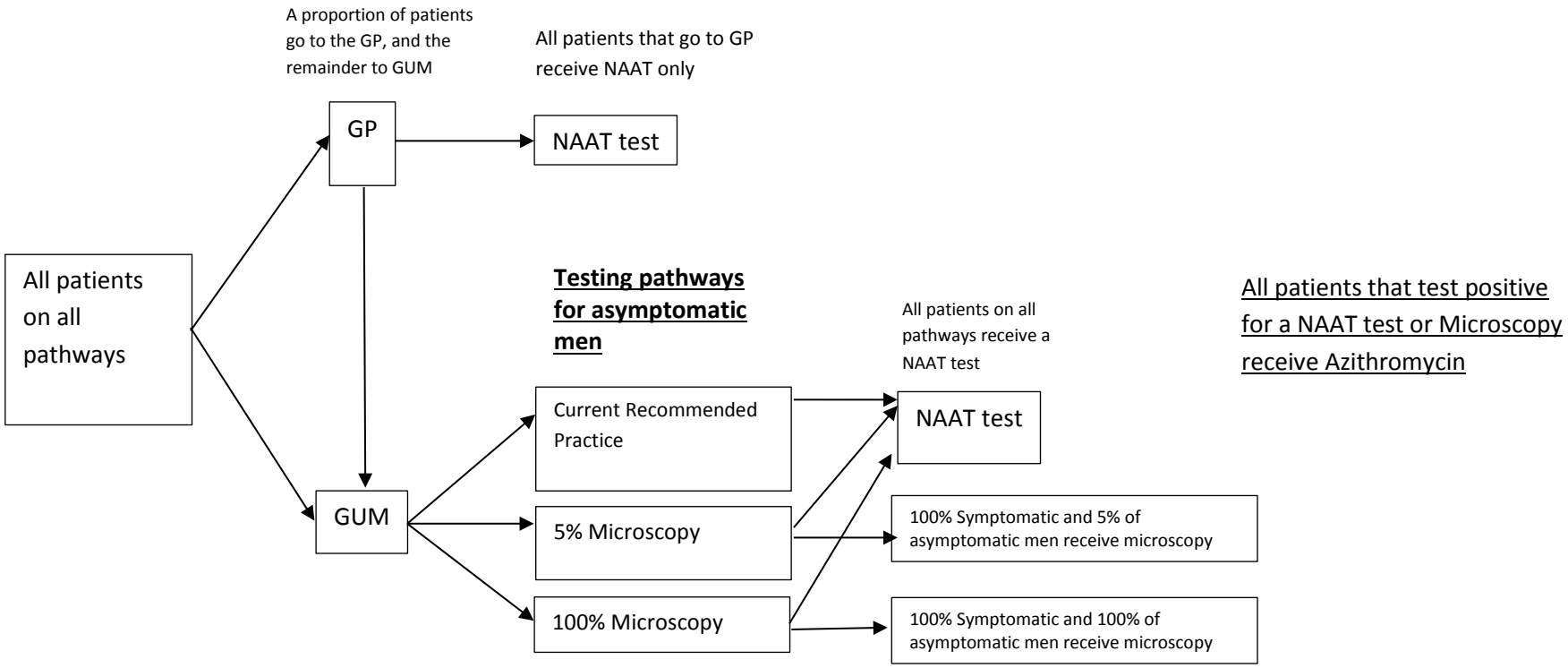

Figure 1: *Flow diagram showing the test and treatment pathway*

Note: NAAT-nucleic acid amplification test for Chlamydia trachomatis & Neisseria gonorrhoeae

Initially, a patient can be either infected or non-infected with *M. genitalium* and either symptomatic or asymptomatic. The patient may attend either a GP or a GUM clinic for testing. For those patients that attend a GP setting, all patients (asymptomatic and symptomatic) are tested for chlamydia and gonorrhoea using nucleic acid amplification test (NAAT) but none are offered microscopy. From the GP setting a proportion of the patients are then referred to a GUM clinic for further investigation and management, for example those who are symptomatic or have more complex sexual health needs.

In contrast, in the GUM setting the diagnostic pathway varies depending on which strategy is being considered and whether the patient presents with symptoms or not. For the 'Current Recommended Practice' strategy, microscopy is not offered to asymptomatic patients and these patients receive a NAAT test for chlamydia and gonorrhoea only. All asymptomatic patients in all locations in the 'Current Recommended Practice' scenario receive a NAAT chlamydia and gonorrhoea only. In the 5% Microscopy and '100% Microscopy' scenarios, 5% and 100% of male patients respectively at GUM clinics receive urethral smear microscopy. During the course of the consultation all symptomatic patients in a GUM setting receive partner notification and condoms with the aim of identifying individuals for whom testing and treatment may be appropriate. The testing pathways considered in this study are shown in Figure 1.

In this analysis, treatment can be deemed either a success or failure. Successful treatment indicates that a patient is no longer infected with *M. genitalium* and cannot transmit infection to their sexual partners. Treatment failure indicates that there has been a failure of the drug treatment to clear *M. genitalium*. Female patients who fail treatment or who are not treated can develop PID, a proportion of which cases are treated. Untreated PID cases may go on to experience symptomatic PID, infertility, or experience an ectopic pregnancy.

Model assumptions and parameterisation

This cost-effectiveness analysis was parameterised through secondary sources which are described below. It was necessary to make some pragmatic clarifying assumptions in order to carry out the analysis, these are described in the Appendix.

The model parameters used in this analysis are shown in Table 1.

Parameter	Value (range)	Reference
Proportion of times HIV test delivered alongside a NAAT test in a GUM setting	83% (range=0.71-0.97)	(8)
Proportion of times syphilis tests delivered alongside a NAAT test in a GUM setting	84% (range=0.72-0.97)	(8)
Proportion PID cases that give rise to ectopic pregnancy	(99/1309) 7.6% (6.4-8.8%)	(9, 10) Based on number trying to conceive after laparoscopy diagnosed PID case. Range calculated from a beta distribution taking values at 5% and 95% parameterised using method of moments (11)
Proportion PID cases that give rise to infertility	18% (15-21%)	(9, 12) range calculated from a beta distribution taking values at 5% and 95% assuming standard error = mean/10 (11)
Proportion of PID cases that are symptomatic	56% (30%-89%)	Value here from Posterior-mean of infectious disease model
Treatment Failure Proportion	0.28	Posterior value from TDM
Delay from PID to infertility / ectopic pregnancy manifest	5 years (1-15years)	Expert opinion – study team

Table 1: *Model parameters used in economic evaluation*

Resource use and costs

The cost of partner notification was adjusted to 2014/15 prices using the pay and price index for Hospital & Community Health Services. Unit staff costs were obtained from Unit Costs of Health & Social Care (2015) (13). The unit costs of each resource used in this economic evaluation are described in the Appendix.

Outcomes

The main outcome measure for this evaluation is the additional cost incurred per case of PID averted. The second outcome measure is the additional cost incurred per major outcome averted (MOA), where a major outcome is defined as a case of symptomatic PID, case of ectopic pregnancy, or a case of infertility. All major outcomes are reported for completeness. The results presented here use the incremental cost-effectiveness ratio (ICER), which is the difference in costs between two options divided by the difference in their effects (which are the outcome measures described above).

Analysis

The base case scenario uses the mean results of 215 parameter sets from the dynamic transmission model and applies resource costs to obtain the baseline deterministic results for each of the three testing scenarios. These deterministic results from the TDM are shown in the Appendix along with details of the sensitivity analysis.

Results

All results presented here are shown for a time horizon of 20 years with discounting unless otherwise stated. In all cases the costs are presented to the nearest thousand, and the outcomes to the nearest hundred. ICER values were calculated using the unrounded cost and outcome values with these then being rounded to the nearest 100.

	Cost	***Cases of PID***	***Major outcomes****	***Symptomatic PID***	***Infertility***	***Ectopic Pregnancy***
No Microscopy	£1,244,736,000	111,800	37,600	23,300	10,000	4,200
5% Microscopy	£1,249,986,000	111,500	37,500	23,200	10,000	4,200
100% Microscopy	£1,350,369,000	105,300	35,600	21,800	9,700	4,100

Table 2: *Baseline results for the three strategies for cases of PID and all the major outcomes considered in this study*

**where major outcomes are symptomatic PID, infertility or ectopic pregnancy*

Outcomes

As shown in Table 2, providing microscopy to 5% of asymptomatic men in a GUM setting has a positive impact on cases of PID. That is, the number of PID cases is lower for 5% Microscopy compared to No Microscopy. Likewise 5% Microscopy coverage also has a positive impact on reducing the number of major outcomes. In the case of the 100%

Microscopy scenario, this has a greater impact on reducing cases of PID and major outcomes compared to either 5% or No Microscopy.

Costs

When only considering costs, it can be seen that the cost of 5% Microscopy coverage is greater than No Microscopy, while 100% Microscopy coverage is the most costly approach. This indicates that any savings that might have been made as a result of a reduction in major outcomes are insufficient to make 5% Microscopy or 100% Microscopy cost saving.

Incremental Results

	Discounted cost	***Cases of PID***	***ICER (/PID averted)***	***Major Outcomes***	***ICER (/MOA)***
No Microscopy	£1,244,736,000	111,800		37,600	
5% Microscopy	£1,249,986,000	111,500	£15,700	37,500	£49,900
100% Microscopy	£1,350,369,000	105,300	£16,300	35,600	£51,900

Table 3: *Incremental cost per case of PID averted and cost per major outcome averted*

For the outcome of a case of PID averted the ICER values are shown in Table 3. It can be seen that 5% Microscopy is more effective than no microscopy and has an ICER of £15,700, meaning that an investment of £15,700 is required to avert one case of PID. For the outcome of MOA it can again be seen (Table 3) that 5% Microscopy is more effective than no microscopy, but in this case an investment of £49,900 is required to avert one major outcome. In the case of 100% Microscopy, an investment of £16,300 is required to avert one case of PID, and £51,900 to avert one major outcome compared to 5% Microscopy.

Sensitivity Analysis

The results of the sensitivity analysis are described in the Appendix.

Discussion

Principal Findings

This economic evaluation utilized the output from a transmission dynamic model (TDM) to estimate whether providing limited microscopy coverage to asymptomatic men to test for NCNGU at a limited number of GUM services (as was the case at the time of the last national audit of practice (1)) is a cost-effective option compared to the recommended current practice of its complete withdrawal.

This economic analysis was based on a principal outcome of cases of PID averted, and a secondary outcome of major outcome averted (MOA) (symptomatic PID, infertility, or ectopic pregnancy). The results at baseline indicate that performing urethral smear microscopy for approximately 5% of asymptomatic men attending GUM has an incremental cost of £15,700 per case of PID averted compared to no microscopy, meaning that this strategy invests approximately £15,700 to avoid one additional case of PID compared to a strategy of no routine microscopy screening where only symptomatic men are tested. Similarly 5% Microscopy coverage requires approximately £49,900 to avert one major outcome compared to a strategy of no routine microscopy screening where only symptomatic men are tested. Hypothetically, if recommended current practice were expanded to performing urethral smear microscopy for 100% of asymptomatic men attending GUM then this would have an additional cost of £16,300 per additional case of PID averted, and an additional £51,900 to avert an additional case of MOA compared to 5% Microscopy. These results also help to show that while conducting microscopy for 5% of asymptomatic men at GUM locations will avert PID and other major outcomes, at a population level it costs more to undertake the microscopy and associated patient management than it does to manage the adverse effects of not preventing the sequelae in a limited number of patients.

Across all the sensitivity analysis undertaken, 5% microscopy coverage was never found to be cost saving but was always found to have a positive impact on reducing cases of PID and major adverse outcomes. Varying the outputs from the TDM provided a range of values for the outcomes in this study. For case of PID averted the ICER values ranged from £9,600-£39,100, while for case of MOA the ICER values ranged from £30,500-£124,400. By varying the time horizon of the analysis it was found that shorter time horizons made the intervention less cost-effective.

Strengths & Weaknesses of Study

This study has utilised the output from a well parameterised dynamic model that describes the transmission of *M. genitalium* in the population of males and females in England aged 16-30 years old. Uncertainty in this model has been considered through the use of multiple parameter sets, while the results from this economic evaluation have been subject to extensive sensitivity analysis. Inevitably this has led to the range of plausible values being obtained from the economic model being quite wide, although this does help to give confidence to the validity of the conclusions that might be drawn from this model.

In this analysis only NCNGU due to M. *genitalium* has been considered in the analysis, and its scope has not been extended to other causes. There are some causes which are innocuous conditions that are not tested for, such as adenovirus which are not known to cause reproductive sequelae in women. Consequently had these non-serious causes been taken into account, then it is very likely that the testing strategies would have been even less cost-effective than has been shown here.

A weakness of this study is the inability to conduct joint probabilistic sensitivity analysis (PSA) for both the economic parameters and the parameters utilized in the transmission dynamic model. Although it was possible to conduct PSA for just the economic parameters while maintaining that output from the TDM at constant values, the results describing the probability of a strategy being below a specific acceptable threshold would be meaningless.

Comparisons with existing studies

To our knowledge this is the first economic analysis related to NCNGU in any setting, and thus comparisons with the results from similar economic studies are impossible.

Meaning of study

It is suggested that UK decision makers are unlikely to fund an intervention if it has an ICER value of £30,000 / quality adjusted life year (QALY) or more (14), meaning that the extra health gain of an intervention as measured in QALYs must not cost more than £30,000 per QALY gained. However, as this study analysed outcomes in terms of cases of PID and major outcomes averted and not in terms of cost per QALY, there are no accepted threshold values which can be used to assess whether providing limited microscopy coverage to asymptomatic men is acceptable or not. This means that if an intervention is more costly and more effective than its comparator, we have no indication of whether the extra effectiveness will be worth

paying for. It is therefore necessary to link the results here to the acceptance threshold values for the QALY in order to draw conclusions from this economic analysis.

Taking mean values from the transmission dynamic model, the ICER for a case of PID averted and MOA were £15,700 and £49,900 respectively for 5% microscopy compared to no microscopy. Using the outcome of case of PID averted as an example, and taking into consideration the maximum acceptance threshold of £30,000 / QALY used by the National Institute of Healthcare and Care Excellence (NICE) in England, for this ICER to be deemed cost-effective based on current accepted thresholds, a case of PID averted would have to result in a gain of 0.53 of a QALY. Alternatively, the implication is that having PID would have to be equivalent to losing more than 6 months of perfect health. Likewise for MOA this would have to be more than 1.67 QALYs, meaning that having a major outcome would have to be equivalent to losing more than 18 months of perfect health.

Even allowing for patient suffering and particularly the stress of infertility, current evidence suggests that these outcomes are not valued so extremely. Smith (15) in a primary study based on a time trade off approach, asked respondents with a previous history of PID to value alternative conditions. The mean valuations for long term health states associated with PID were: ectopic pregnancy 0.79 (SD=0.34); pelvic pain 0.69 (SD=0.37); Infertility 0.76 (SD=0.34). These values suggest that the mean QALY gain to avert a case of pelvic pain (the state with the reported greatest negative impact on QoL) that lasted one year would be 0.31 QALYs. However as noted above for the results described here, for 5% microscopy coverage to be cost effective, a MOA must lead to a gain of more than 1 QALY, suggesting that the current practice of providing limited microscopy coverage for asymptomatic men is far from being cost-effective.

Given the comparisons described above, it can therefore be concluded that the recommended practice of reserving urethral microscopy for symptomatic men and not testing asymptomatic men is a cost-effective strategy and reintroducing ad-hoc testing for asymptomatic men in GUM locations is unlikely to be cost-effective. Considering the results at baseline in this study, if ad-hoc microscopy testing for asymptomatic men were reintroduced into GUM locations then this would lead to over £5,000,000 (discounted) in costs over a 20 year period, which could then be better spent expanding testing and treatment regimens for different diseases which are more cost-effective. However the results shown in this study do very much represent the current situation in terms of testing for M. *genitalium*, indeed, as diagnostic technology moves forward, it is likely that routine screening for M. genitalium

will become more viable in terms of its effectiveness at improving patient outcomes and cost-effectiveness.

Unanswered questions and future research

One of the major issues related to any testing and diagnosis strategy is the impact of the testing pathway on patients. Patients may suffer from anxiety while waiting for the result of a test, or may incur societal costs as a result of having to take time off work to attend for testing. There are also issues specific to the context of sexually transmitted infections where patients may be worried about the stigma of attending for testing and the difficulties surrounding partner notification for NCNGU. In the testing and diagnosis context, future work should focus on these issues, in order to better quantify their impact on patients with the goal of including the impact of these issues in economic studies such as this in order to better describe the true impact of the complete testing pathway on patients. Furthermore, this study has not considered the possibility of targeting high risk asymptomatic males with a NAAT for M. *genitalium*, e.g. males that have a sexual partner with risk factor for STI, males that undertake high-risk sexual behaviour, or males that have had sexual contact with persons with an STI or PID. This could be considered in future work, since targeting these individuals is likely to have a positive impact on disease transmission and therefore cost-effectiveness. Finally, we recognise that our understanding of the urethral microbiome and the significance of micro-organisms found in the male urethra is incomplete. It may be that other organisms also cause male urethritis and are associated with adverse reproductive consequence in women. As information becomes available, future work can take this new knowledge and update our approach to provide more robust cost-effectiveness estimates.

Key Messages

- Current clinical recommendations for the UK are that urethral microscopy should not be offered to asymptomatic men attending genitourinary medicine clinics for diagnosis of NCNGU
- Offering Microscopy at very low level of coverage where a small number of GUM services in England routinely offered asymptomatic men urethral microscopy for NCNGU is not cost-effective and wastes resources which could be put to better use elsewhere
- Complete withdrawal of microscopy testing for asymptomatic men in a GUM setting could save over £5,000,000 (discounted) over a 20 year period

Funding

This paper presents independent research commissioned by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research scheme (RP-PG-0707-10208). In addition, PJW thanks the UK Medical Research Council for Centre funding (grant MR/K010174/1) and also thanks the UK National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Modelling Methodology at Imperial College London in partnership with Public Health England (PHE) for funding (grant HPRU-2012-10080). AJS was supported by the National Institute for Health Research Diagnostic Evidence Co-operative Leeds.

The views expressed in this paper are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health, or Public Health England. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Cost-effectiveness of abandoning microscopy of urethral smears for asymptomatic non-chlamydial non-gonococcal urethritis in men in the UK

Appendix 1

Model Assumptions

All assumptions were confirmed and agreed with clinical experts within the team before the analysis was carried out. The following assumptions were made:

- Symptomatic patients are index patients with symptoms due to their underlying infection
- An HIV and syphilis blood test is administered 5% of the time in a GP setting (expert opinion)
- All patients in all settings receive a NAAT test for Chlamydia and Gonorrhoea

- A GP consultation takes 11.7 minutes which is the average for a surgery consultation (13)
- All patients in a GUM setting are seen 50% by a doctor and 50% by a band 7 (clinical specialist) nurse (Expert opinion)
- Partner notification is conducted with all symptomatic patients in a GUM setting by a band 7 nurse and this takes 12 minutes (16)
- No formal partner notification is conducted in a GP setting, with just brief 'words of advice' to encourage sexual partners to attend for testing and treatment being given which was not considered in this economic analysis
- Taking case history takes 5 minutes for asymptomatic patients in a GUM setting (Expert opinion – study team)
- Taking case history takes 10 minutes for symptomatic patients in a GUM setting (Expert opinion – study team)
- Examination of a female patient in a GUM setting takes 10 minutes (Expert opinion – study team)
- Examination of a male patient in a GUM setting takes 5 minutes (Expert opinion – study team)
- A single dose (1g) of azithromycin is given as treatment for NGNCU
- For all microscopy tests implemented it takes 10 minutes for a lab technician to obtain and report the results of the microscopy test (Expert opinion – study team)
- The treatment for PID considered in this study is intramuscular ceftriaxone 500mg single dose followed by oral Doxycycline 100 mg twice daily plus metronidazole 400mg twice daily for 14 days (17)
- All notified partners are assessed and presumptively treated in a GUM location and are asymptomatic (Expert opinion – study team)
- The cost of PID does not include the cost of assisted reproduction

Resource Use and Costs

The ranges for the costs were taken by firstly describing the variation in the length of time of the procedures through the use of a gamma distribution with the mean = standard error and taking the values at the 5% and 95% points (with the minimum consultation time set to 2 minutes). And then secondly where more than one member of staff is assumed to contribute to an examination the cheapest and more expensive members of staff would be assumed to

conduct the examination for the low and upper values of the range respectively. Some costs are unit costs and as such have a fixed cost that does not vary.

Resource	Unit Cost	Range	Source
NAAT nucleic acid amplification test - "NAAT"	£9.27		£7.35 for a swab 2005 prices = cost of hands-on time + equipment and consumables cost per test [7]
HIV test	£8.47		Rapid test kit £5-£11 (18) (mid-point 2014/15 prices)
Syphilis test	£2		EIA Assume £2
Microscopy test (including staff costs)	£7		NHS reference costs 2014-15 HRG DAPS07 Microscopy
Lab Technician (10 minutes of staff time) to obtain and report results of microscopy test	£3.33	£0.67-£10	Clinical support worker nursing (community) £20 /hr (13) (Range 2min-30min)
Staff time to give results for Microscopy at Genitourinary Medicine (5 minutes of staff time)	£6.75	£2.70-£20.25	5 minutes with Nurse advanced (£81 / hour) (13) (Range 2min – 15min)
Azithromycin – drug cost for treatment	£6.44		BNF accessed 21st June 2016 250mg tablets 4-tab pack £6.44
General Practice visit (excluding testing costs)	£44	£7.50-£131.25	GP includes direct care staff costs (with qualification costs, £225/hr) Assume 11.7 min surgery consultation (13) (Range 2min-35min)
Cost of Partner Notification in GUM setting – administered to all symptomatic patients	£16.2	£2.70-£48.60	12 minutes with Nurse Advanced (£81 / hour (13) (Range 2min-36min)
Partner Notification leaflets + condoms given out during partner notification	£1.00		Assumed cost
Asymptomatic female at GUM clinic - Case history + Exam (13 minutes of staff time) 50% with Band 7 nurse and 50% with GP	£27.30	£2.70-£111.15	Nurse advanced cost per hour in surgery excluding qualification costs (£81 / hour) '+ GP excluding direct care staff costs (without qualification costs) (£171 / hr patient contact) (13) (Range 2min – 53min)
Symptomatic female at GUM clinic - Case history + Exam (18 minutes of staff time) 50% with Band 7 nurse and 50% with GP	£37.80	£1.35-£153.90	“” Range (2min-73min)
Asymptomatic male at GUM clinic – Case history + Exam (10 minutes of staff time) 50% with Band 7 nurse and 50% with GP	£21	£2.70-£85.50	“” Range (2min-41min)
Symptomatic male at GUM – Case history + Exam (15 minutes of staff time) 50% with Band 7 nurse and 50% with GP	£31.50	£2.70-£128.25	“” Range (2min-62min)
Cost of treating PID	£14.52		Ceftriaxone 500mg single dose, (1g vial) £9.58; Doxycycline 100mg twice daily for 14 days 100mg 8-cap pack £0.55 x 4; and Metronidazole 400mg twice daily for 14 days, 21-tab pack £1.37 x 2
Ectopic Pregnancy	£436.48		MA18C medical termination of pregnancy – less than 14 weeks gestation, elective inpatient NHS ref costs 14-15
Infertility	£587.02		£428 in 2003 (16) Using the hospital and community health services (HCHS) index to inflate to 2014 price 2002/03 index = 213.7 2014/15 index = 293.1. One cycle of treatment assumed per case

Table 2: *Resource use and costs*

Sensitivity Analysis

Two scenarios were examined to assess the impact of increasing and decreasing the costs applied in the study as follows:

- Minimize costs - All costs are set to a minimum by taking the lowest realistic length of time for all consultations in all settings (minimum 2 minutes). Where two staff members undertake a consultation at baseline, in this scenario only the lowest paid is assumed to carry out the consultation.
- Maximize costs – All costs are set to a maximum by taking the highest realistic length of time for each consultation. Where two staff members undertake a consultation at baseline, the highest paid of the staff members is assumed to carry out the entire consultation.

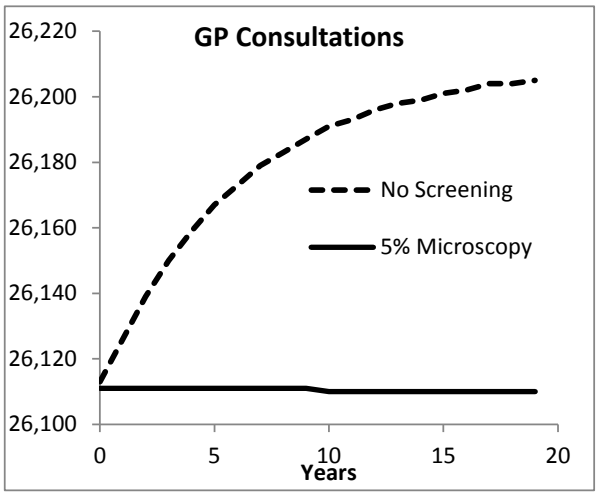
In addition, three further outputs from the transmission model were also analysed to assess their impact on the model results. These were median results (Median) from the 215 parameter sets of the transmission dynamic model, and the upper (Upper) and lower (Lower) results from the 95% range of values.

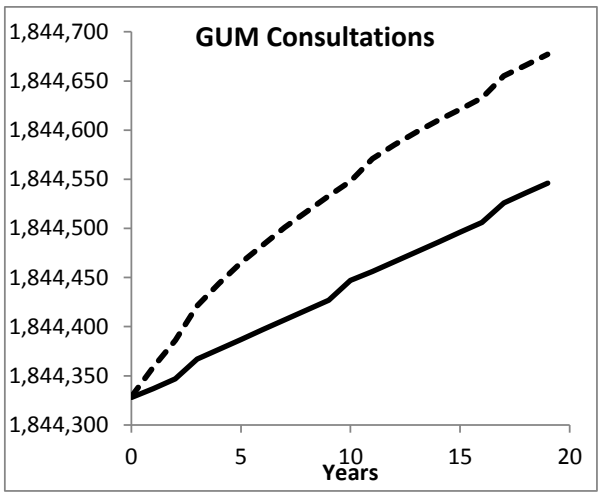
Further one-way sensitivity analysis of key parameters was also investigated, with particular attention paid to parameters that were estimated through expert opinion. In addition the time horizon was also varied to show its impact on conclusions drawn from the model.

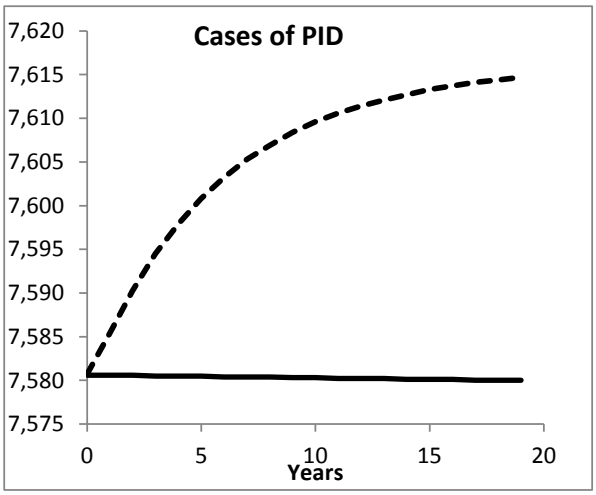
Appendix II

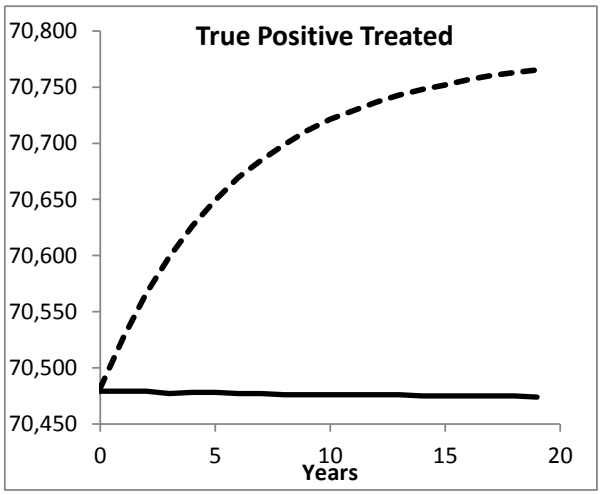
Mean Output from the Transmission Model

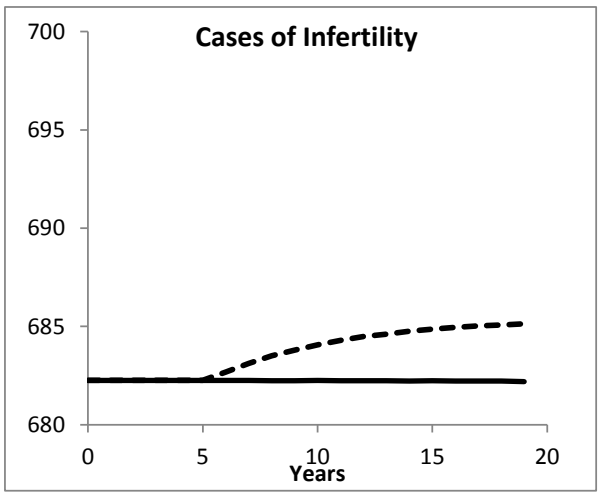
The following graphs provide a summary of the mean output from the transmission model which was utilized in this economic analysis at baseline for each of the two scenarios considered in this study.











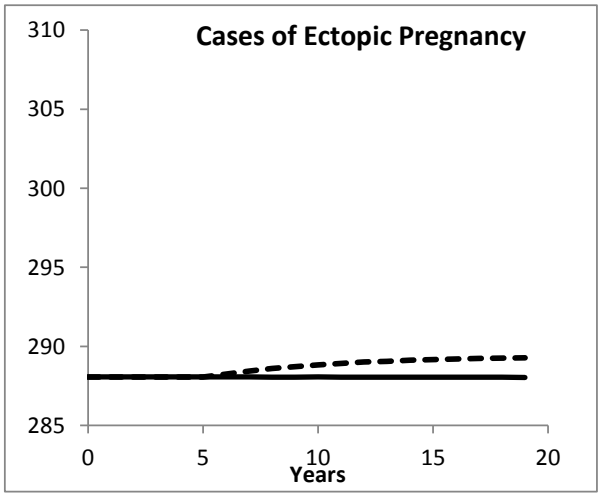


Figure A1: *Output from the transmission model used in the baseline economic analysis with variation in the testing strategy*

It can be seen from Figure A1 that increasing the coverage of microscopy leads to an increase in the annual number of consultations in both GP and GUM locations. Moreover this increasing coverage also has a positive impact on reducing the number of cases of PID averted, the number of cases of infertility, and the number of cases of ectopic pregnancy. It also lowers the number of true positive patients with NGNCU being treated, due to its impact on onward transmission.

Appendix III

Sensitivity Analysis -Results

The two scenarios examined in this study consider the impact of reducing and increasing multiple cost parameters to see their cumulative impact on the results obtained from the model.

Parameter	**ICER /PID averted**	**ICER /MOA**
Maximize Costs	£34,000	£108,500
Minimize Costs	£9,600	£30,500

Table A1: *Sensitivity analysis results for the alternative cost scenarios for No Microscopy vs. 5% Microscopy*

As shown in Table A1, by varying the costs applied in the model it can be seen that for No Microscopy vs. 5% Microscopy the ICER for PID averted ranges from £9,600-£30,500 while the ICER for MOA ranges from £34,000-£108,500.

Variations in Transmission Model Output

The sensitivity analysis above has only considered uncertainty in the parameters used in the economic evaluation and has until now only adopted mean values from the infectious disease model. In order to examine how uncertainty in the output from the infectious disease model affects the conclusions drawn from the economic model, a further series of outputs from the infectious disease model were also considered, these being the median results obtained from the 215 parameter sets along with upper and lower limits informed by the 95% ranges.

Dynamic transmission model output scenario	***ICER No Microscopy vs. 5% Microscopy Cost / Case of PID averted; Cost/ MOA***
Mean	£15,700; £49,900
Median	£39,100; £124,400
Upper	£30,400; £95,400
Lower	£10,800; £34,600

Table A2: ICER values for the outcomes of case of PID averted and major adverse event averted with variation in the infectious disease model output

By examining that impact of various plausible outputs from the TDM (Table A2), it can be seen that the range of ICER values for No Microscopy vs. 5% Microscopy for the outcome measure of case of PID averted treated range from £10,800-£39,100 and for major outcome averted range from £34,600-£124,400.

Time Horizon

In order to investigate the impact of the time horizon on the model results, the results from a range of alternatives are considered here. Table A3 shows the impact of varying the time horizon on the cost, the number of PID cases averted, and MOA. It can be seen that in the short term limited microscopy is least cost effective, but the intervention becomes more cost-effective the further the time horizon is extended into the future.

Time Horizon	*Scenario*	*Cost*	*Cases of PID*	*ICER (PID case averted)*	*Major Outcomes*	*ICER (/MOA)*
5 years	No Microscopy	£395,381,000	35,500		11,900	
	5% Microscopy	£397,087,000	35,400	£41,000	11,900	£146,600
10 years	No Microscopy	£728,324,000	65,400		22,000	
	5% Microscopy	£731,433,000	65,300	£22,600	22,000	£76,800
15 years	No Microscopy	£1,008,676,000	90,600		30,500	
	5% Microscopy	£1,012,950,000	90,400	£17,800	30,400	£57,900
20 years	No Microscopy	£1,244,736,000	111,800		37,600	
	5% Microscopy	£1,249,986,000	111,500	£15,700	37,500	£49,900

Table A3: *Deterministic results for each of the outcomes considered in this study with variation in the time horizon*

One-way sensitivity Analysis

The parameters, proportion of PID cases that are symptomatic and the delay from PID to infertility / ectopic pregnancy manifest were informed by expert opinion in this study, and as such it is necessary to examine their impact on the results from the model. Neither of these parameters had an impact on the ICER values for the main outcome measure used in this study, namely, cases of PID averted, but can impact on MOA. This is shown in the table A4.

Parameter	ICER /PID averted	ICER /MOA
Delay from PID to Infertility / ectopic pregnancy		
1 years	£15,600	£47,200
2	£15,700	£47,900
3	£15,700	£48,600
5 (Baseline)	£15,700	£49,900
10	£15,700	£52,900
15	£15,700	£55,300
Proportion of PID cases that are symptomatic		
20%	£15,700	£96,900
40	£15,700	£63,600
56 (Baseline)	£15,700	£49,900
60	£15,700	£47,400
80	£15,700	£37,700
100	£15,700	£31,300

Table A4: *Results from one-way sensitivity analysis for No Microscopy vs. 5% Microscopy*

It can be seen that varying these parameters has very little impact on the ICER values for the primary outcome measure of cost / case of PID averted. In the case of MOA, for the parameter estimated time to infertility / ectopic pregnancy manifest, as this is increased, 5% Microscopy becomes increasingly less cost-effective. For the proportion of PID cases that are symptomatic, increasing this value leads to the ICER values for MOA to decrease, thus making 5% Microscopy more cost-effective.

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